(ii) assigning the exact numerical migration value to the test duplex based on the relative migration position of the test duplex compared to the migration value of the control duplex.

A marked up version of the amendment showing additions in bold and underline and deletions in bold and brackets is attached hereto.

REMARKS

Claims 55-69 and 73-76 are pending in this application. Claims 70-72 have been cancelled without prejudice as a result of a restriction requirement imposed in the application. Claims 55 and 73 have been amended to recite features that were previously inherent in the claims, namely that the exact migration value is numerical in nature and the database is independent of the actual separation performed on the duplex molecules. Claim 60 has been broadened by depending from a broader claim and reciting all mammalian MHC genes instead of just HLA alleles. Claim 61 has been broadened by removing any qualifications regarding the type of HLA alleles and thus the claim covers all HLA alleles. Claim 76 has been amended to harmonize the terms to those used in claim 73.

Applicants would like to thank the Examiner for the telephonic interview of December 13, 2001. In the Interview all of the outstanding rejections were discussed although no general agreement was reached concerning the allowability of the claims.

The specification has been amended to correct a minor typographical error and add SEQ ID NOS. Support for the claim amendments can be found in numerous places throughout the application as filed, including, but not limited to:

Claim 55: FIGS. 8-15B (showing numerical migration values and databases of values independent of the separations);

Claim 60: Page 17, lines 24-25 ("Examples of genes with multiple alleles to which the invention may be applied are the mammalian MHC genes..."); and

Claim 73: FIGS. 8-15B (showing numerical migration values and databases of values independent of the separations).

The present amendment adds no new matter and is thus proper. Entry of this amendment in its entirety is therefore requested. Because the amendments either broaden the claims, make explicit what was inherent or do not change the scope of the claims, the claim amendments are not narrowing and accordingly the claims are entitled to the same, or broader, scope either literally or under the Doctrine of Equivalents.

In view of the amendments and following remarks, reconsideration and withdrawal of the rejections to the application in the Office Action is respectfully requested.

I. Specification

The Office Action noted that the CRF previously submitted by applicants had errors which prevented it from being entered. A new CRF is being sent on the same day as this Amendment and Response to the address: U.S. Patent and Trademark Office, BOX SEQUENCE, P.O. Box 2327, Arlington, VA 22202. The Office Action also noted that the specification had not been amended to include the required sequence identifiers. Applicants have amended the specification to include the required sequence identifiers. These amendments and submissions place the instant application in compliance with 37 CFR §§1.821-1.825.

The Office Action also required submission of a substitute specification excluding the claims. A substitute specification prior to any amendments is submitted herewith.

II. Claim Objection

Claim 73 was objected to for reciting step (1) between steps (e) and (g). Claim 73 has been amended to recite (f) in place of (1). Applicants thus respectfully request withdrawal of this claim objection.

III. Rejections Under 35 U.S.C. §112, First Paragraph

Claims 55-69 and 73-76 were "rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Specifically, the Office Action stated "[i]n the instantly rejected claims, the new limitation of 'exact migration value' in claims 55-69 and 73-76 appears to represent new matter. Furthermore, the new limitations in claims 65 and 76 appear to represent new matter."

The phrase "exact migration value" has been amended to recite "exact numerical migration value[.]" Regarding this phrase, applicants would like to draw the Examiner's attention to page 26, lines 4-8 of the application which states "[t]hese labeled markers would be either defined segments of genomic DNA prepared by amplification or synthetically prepared so as to act as reference points for automatic computation of the *exact* position of the sample under investigation." It is well known in the art that the positions to which molecules move in a separation analyses are referred to as "migration values." This fact is clearly evidenced throughout the specification by the above passage ("exact position") as well as numerous other places including page 41, lines 1-6, which states in pertinent part "relative *value*, is the *measure* of the *migration* of the bands... The *values* of the *migration* of the subsequent bands are calculated from this curve." Clearly then the present application embodies the concept of an "exact numerical migration value[.]" Examples of such exact numerical migration values can be found throughout the specification as exemplified by Tables 2-3 and FIGS. 8-15B. In fact tables 2 and 3 not only provide exact numerical migration values they also provide the standard deviation for these values based on several different separations.

Moving to claim 65 the Office Action further stated "Applicant did not provide a page number for the basis of the limitation in claim 65[.]" Applicants apologize for this oversight and would like to the point the Examiner's attention to page 1, lines 3-6 as support for claim 65. This passage states "[t]he invention relates to methods for separating and

identifying DNA molecules in mixtures of DNA molecules *having the same number of nucleotides* but different base sequences."

With respect to claim 76 the Office Action stated "the two step process provided in claim 76 does not appear to be provided for in the specification." The two step process of claim 76 recites "(i) assigning a migration value to the at least one control duplex; and (ii) assigning the exact numerical migration value to the test duplex based on the relative migration position of the test duplex compared to the migration value of the control duplex." Applicants are unsure why the paragraph at page 41, lines 1-7 does not provide support for this claim. This paragraph states:

> RV = relative value, is the measure of the migration of the bands. It is arrived at by using the positions of the front running primer band and the reference homoduplex (values 1 and 1000 respectively) in each track, to compute a standard curve. The values of the migration of the subsequent bands are calculated from this curve.

Clearly, this paragraph describes "assigning a migration value to the at least one control duplex" by stating "the positions of the front running primer band and the reference homoduplex (values 1 and 1000 respectively)[.]" The other step is also clearly provided for by the statement that "[t]he values of the migration of the subsequent bands are calculated from this curve" which is computed from "the positions of the front running primer band and the reference homoduplex (values 1 and 1000 respectively)[.]" Additional support for this claim can be found at page 24, lines 23-32 which states in pertinent part "[t]he position of the identified bands... can be accurately assigned by the inclusion of reference mobility markers[.]" Claim 76 merely rephrases the concepts described in these, and other passages, in language more appropriate for a claim. As stated in the MPEP "**[m]ere rephrasing** of a passage does **not** constitute new matter. Accordingly, a rewording of a passage where the same meaning remains intact is permissible." MPEP §2163.07 (emphasis added)(citations omitted).

Based on the above citations, applicants respectfully request the Examiner withdraw these rejections.

IV. Rejections Under 35 U.S.C. §112, Second Paragraph

"Claims 55-69 and 73-76 [we]re rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Specifically:

> it is not clear if an 'exact migration value' can be considered the consistent location a specific duplex on a gel, thus a visual assessment and comparison of the duplex in the gel represents the assignment of an exact migration value, or if an 'exact migration value' requires that some numeric value be associated with the migration of a duplex.

As used in the present claims, applicants submit that it is clear to the skilled artisan that an "exact migration value" requires the assignment of an numerical value to the position to which the duplexes migrate as any "value" in the scientific sense is fundamentally numerical in nature. This is clearly evidenced by a common dictionary definition of "value" as "a numerical quantity that is assigned or is determined by calculation or measurement[.]" Merriam Webster's Collegiate Dictionary 1305 (Tenth Ed. 1997). Accordingly, the claims have been amended to recite the inherent characteristic that a value is numerical in nature.

Claim 59 was rejected "because it recites a list of arbitrary abbreviations representing gene names which are not defined in the claim or specification." Applicants respectfully disagree with this rejection because there is nothing arbitrary about the abbreviations recited in claim 59. In fact all of the abbreviations are not only well known to those skilled in the art, they were in fact given those abbreviations by those same artisans. This fact is plainly evident not only from the references referred to in the application in relation to those abbreviations but also from a cursory search of the art. Accordingly, because one skilled in the art would recognize what the abbreviations in claim 59 stand for, "the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice functions required by 35 U.S.C. 112, second paragraph." MPEP §2173.02.

Claim 61 was rejected as "indefinite over the recitation of 'mammalian HLA alleles and human HLA alleles' because the claim is confusing." Claim 61 has been amended to recite "HLA alleles" with no qualifications rendering the rejection moot.

Claim 73 was rejected as "indefinite because the phrase 'single stranded DNA' lacks proper antecedent basis in the claim." Claim 73 has been amended to provide proper antecedent basis for the phrase.

In light of the above amendments and arguments, applicants respectfully request the Examiner withdraw these rejections.

V. Rejections Under 35 U.S.C. §102

Claims 55-67, 69, and 73-76 were "rejected under 35 U.S.C. 102(b) as anticipated by Zimmerman *et al.* (Nucleic Acids Research, 1993, Vol. 21, No. 19, 4541-4547)." (Zimmerman *et al.*) "This rejection applies to these claims wherein assigning an exact migration value is interpreted to mean the consistent location of a specific duplex on the gel, thus a visual assessment and comparison of the duplex in the gel represents the assignment of an exact migration value." Applicants have amended the claim to provide that the value is numerical in nature and thus the above interpretation is not applicable to the present claims. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

VI. Rejections Under 35 U.S.C. §103

Claim 68 was rejected "under 35 U.S.C. 103(a) as being unpatentable over Zimmerman *et al.*" As above, "[t]his rejection applies to these claims wherein assigning an exact migration value is interpreted to mean the consistent location of a specific duplex on the gel, thus a visual assessment and comparison of the duplex in the gel represents the assignment of an exact migration value." Applicants have amended the claim to provide that the value is numerical in nature and thus the above interpretation is not applicable to the present claims. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Claims 55-59 and 73-76 were:

> rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmerman *et al.* in view of Mullins *et al.* (WO 95/01453). This rejection applies to the claims when 'exact migration value' is interpreted to require the assignment of a numerical value to the distance traveled by the

> heteroduplexes...
>
> Zimmerman *et al.* demonstrate the use of their method for the determination of HLA DQA1 type for a family. In order to do so, they run the heteroduplexes out on an electrophoretic gel, assess the positions of the bands, compare the test duplexes to a database of reference duplexes. The left side of the gel in Figure 3 is considered to be a database of test duplex migration values.
>
> Zimmerman *et al.* do not assign an 'exact migration value' to the distance traveled by the heteroduplexes, wherein such a value requires that some numerical value be assigned to the distance traveled ...
>
> Mullins *et al.*, in example 4, provide methodology and examples of the assignment of exact numeric hierodule mobility migration values.

As stated in the MPEP:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation... to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest **all** the claim limitations.

MPEP §2143 (emphasis added).

Applicants respectfully submit that the present rejection does not state a proper prima facie case of obviousness because the combination does not teach or suggest all of the claim limitations. Applicants believe this rejection is also based on a misunderstanding of the cited references and the claimed invention. The Examiner explicitly admits that "Zimmerman *et al.* do not assign an 'exact migration value' to the distance traveled by the heteroduplexes[.]" It automatically follows that Zimmerman *et al.* cannot disclose the step of identifying a heteroduplex by matching the exact numerical migration value of the heteroduplex with the migration value of a known DNA molecule because nowhere do Zimmerman *et al.* assign such values.

Additionally, Zimmerman *et al.* do not disclose a database of migration values of identified DNA molecules as required by the instant claims. To the skilled artisan a database is generally known as a "large collection of data organized especially for rapid search and retrieval (as by computer)." Merriam Webster's Collegiate Dictionary 293 (Tenth Ed.

1997). Intrinsically, any database would be separate and apart from a physical separation performed on heteroduplexes and the claims have been amended to reflect this necessity. Thus the skilled artisan would not consider "[t]he left side of the gel in Figure 3...to be a database of test duplex migration values" because the left side of the gel does not contain "large collection of data organized especially for rapid search and retrieval" nor is the database separate and apart from the physical separation assay. Instead one skilled in the art would recognize the left side of the gel in figure 3 for what it is - a limited number of positive controls against which the heteroduplexes must be matched on the gel to identify the DNA molecules in the heteroduplex.

In order to positively identify a truly unknown HLA allele in an individual, Zimmerman *et al.* would have to run well in excess of 100 positive controls to identify the unknown allele. *See* Zimmerman *et al.* which notes on page 4541 that the HLA*DRB1, HLA*DQA1, HLA*DQB1, HLA*DPA1 and HLA*DPB1 genes contain 66, 10, 13, 4 and 26 separate alleles, respectively, for a grand total of 119 different alleles. These are only a fraction of the known HLA alleles which number in the hundreds, if not thousands. Schreuder *et al.*, Tissue Antigens, 58:109 (2001)(abstract enclosed).

Mullins *et al.* do not overcome this deficiency because nowhere do Mullins *et al.* teach a database having migration values. Additionally, applicants respectfully disagree that Mullins *et al.* teach a method for "assigning an exact numerical migration value to the position to which the test duplex migrates" which can be used to "identify the DNA molecule[.]" Mullins *et al.* is not directed to identifying duplex DNA molecules, but is instead focused entirely on sequence diversity, that is how many differences exist between DNA molecules. Mullins *et al.* is only directed at determining how numerous differences between two DNAs are, not the identity of the actual differences. In fact, Mullins *et al.* state their "method allows the determination of sequence relatedness **without** resorting to sequencing analysis[.]" Page 22, lines 17-19. It does not matter in the method of Mullins *et al.* what base a certain base is replaced with, it only matters that the certain base is replaced, removed, etc. For example if a certain position normally is occupied by an A, the methods of

Mullins *et al.* only determine if the A is replaced or removed, not whether it is replaced with a C, G or T. Thus any numerical value Mullins *et al.* places on a duplex migration cannot actually identify a DNA sequence, only how genetically divergent those sequences are. This is clear from the exact passage cited in the Office Action for the proposition that Mullins *et al.* "in example 4, provide methodology and examples of the assignment of exact numeric hierodule mobility migration values." In example 4 of Mullins *et al.* migration values "were calculated as the **average** distance of migration of the **two** heteroduplex bands divided by the distance of migration of the homoduplex bands. The sequence **divergence** between the nucleic acid sequences from each HIV-fragment were determined..." Page 50, line 37 through page 51, line 4. Because the migration values are based on an "average distance of **two** heteroduplex bands" the migration value relates to both of these heteroduplexes and is not specific for either one of the heteroduplex bands separately. Thus, any migration value calculated in Mullins *et al.* is simply not capable of providing for the positive and actual identification of any of the DNA molecules in the heteroduplex bands as is required by the instant claims.

Thus, a combination of Zimmerman *et al.* with Mullins *et al.* cannot make the claimed invention obvious. Neither Zimmerman *et al.* nor Mullins *et al.* teach a method for "assigning an exact numerical migration value to the position to which the test duplex migrates" or "identifying the DNA molecule by matching the exact migration value with a database of migration values of identified DNA molecules, wherein the database of migration values is independent of the separation." Accordingly, applicants respectfully request the Examiner withdraw the rejection because the references, alone or in combination, do not teach or suggest all of the claim limitations.

VII. Conclusion

In view of the forgoing amendments and remarks, it is respectfully submitted that this application is in condition for allowance and thus an early indication of allowance is solicited. If the Examiner has any questions, or believes a telephone discussion would expedite the prosecution of this application, she is invited to contact the undersigned at (608) 258-4272.

Respectfully submitted,

April 5, 2002
Date

Mark A. Kassel, Reg. No. 38,200
Attorney for Applicant
Foley & Lardner
150 East Gilman Street
Post Office Box 1497
Madison, Wisconsin 53701-1497
(608) 258-4272

Version with markings to show changes made.

In the Specification:

Paragraph starting on page 12, line 26, and ending on page 12, line 31:

The complementary strand of the reference DNA molecule may be provided by essentially the same technique as the technique set out above in steps (i) to (iv) for providing the mixture of DNA molecules in single-**stranded [standard]** form. In particular, the reference complementary strand DNA molecule may be provided by

Paragraph starting on page 26, line 1:

This approach is suitable for automated separation and detection. In order to automate the analysis, it is proposed to include mobility markers in the separation phase. These label**[l]**ed marke**r**s would be either defined segments of genomic DNA prepared by amplification or synthetically prepared so as to act as reference points for automatic computation of the exact position of the sample under investigation.

Paragraphs starting on page 35, line 8, and ending on page 35, line 24:

5' A locus primer: GAA ACG/C GCC TCT GT/CG GGG AGA AGC AA (Intron 1: 21-46) **(SEQ ID NO:1)**

3' A locus primer: TGT TGG TCC CAA TTG TCT CCC CTC (Intron 3: 66-89) **(SEQ ID NO:2)**

5' B locus primer: GGG AGG AGC GAG GGG ACC G/CCA G (Intron 1: 36-57) **(SEQ ID NO:3)**

3' B locus primer: GGA GGC CAT CCC CGG CGA CCT AT (Intron 3: 37-59) **(SEQ ID NO:4)**

5' C locus primer: AGC GAG GG/TG CCC GCC CGG CGA (Intron 1: 42- 61) **(SEQ ID NO:5)**

3' C locus primer: GGA GAT GGG GAA GGC TCC CCA CT (Intron 3: 12-35) **(SEQ ID NO:6)**

Paragraph starting at page 41, line 1:

RV = relative value, is the measure of the migration of the bands. It is arrived at by using the positions of the front running primer band and the reference homoduplex (values 1 and 1000 respectively) in each track, to compute a standard curve. The values of the migration of the subsequent bands **[is]** **are** calculated from this curve. RV is followed by SD for each set of tests.

In the Claims:

55. (Amended) A method for identifying a DNA molecule comprising:

(a) hybridizing a single strand DNA molecule with a complementary reference DNA strand to form a test duplex;

(b) separating the test duplex from at least one control duplex run in the same separation;

(c) detecting the positions to which the test duplex and the at least one control duplex migrate in the separation;

(d) assigning an exact **numerical** migration value to the position to which the test duplex migrates; and

(e) identifying the DNA molecule by matching the exact migration value with a database of migration values of identified DNA molecules**, wherein the database of migration values is independent of the separation**.

60. (Amended) The method of claim **[59]** **55** wherein the database of migration values comprises migration values for **mammalian MHC genes** **[HLA alleles]**.

61. (Amended) The method of claim [60] **59** wherein the **[HLA]** alleles are selected from the group consisting of **[mammalian HLA alleles and human]** HLA alleles.

73. (Amended) A method for identifying a DNA molecule, comprising:

(a) amplifying a DNA molecule to produce amplified double stranded DNA molecules;

(b) denaturing the amplified double stranded DNA molecules into **single** stranded DNA molecules wherein the single stranded DNA molecules include sense and antisense strands;

(c) hybridizing the single stranded DNA molecules with reference DNA strands which are complementary to the single stranded DNA molecules to form test duplexes;

(d) separating the test duplexes from at least one control duplex run in the same separation;

(e) detecting the positions to which the test duplexes and the at least one control duplex migrate in the separation;

[(1)] (f) assigning an exact **numerical** migration value to the position to which the test duplex migrates; and

(g) identifying the DNA molecule by matching the exact migration with a database of migration values of identified DNA molecules**, wherein the database of migration values is independent of the separation**.

76. (Amended) The method of claim 73 wherein step (f) comprises:

(i) assigning a migration value to the at least one control duplex; and

(ii) assigning the exact **numerical** migration value to the test duplex based on the relative migration position of the test duplex compared to the migration value of the control duplex.